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Delirium is associated with early postoperative cognitive dysfunction

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Summary

The purpose of this analysis was to determine if postoperative delirium was associated with early postoperative cognitive dysfunction (at 7 days) and long-term postoperative cognitive dysfunction (at 3 months). The International Study of Postoperative Cognitive Dysfunction recruited 1218 subjects ≥60 yr old undergoing elective, non-cardiac surgery. Postoperatively, subjects were evaluated for delirium using the criteria of the Diagnostic and Statistical Manual. Subjects underwent neuropsychological testing pre-operatively and postoperatively at 7 days (n = 1018) and 3 months (n = 946). Postoperative cognitive dysfunction was defined as a composite Z-score >2 across tests or at least two individual test Z-scores >2. Subjects with delirium were significantly less likely to participate in postoperative testing. Delirium was associated with an increased incidence of early postoperative cognitive dysfunction (adjusted risk ratio 1.6, 95% CI 1.1–2.1), but not long-term postoperative cognitive dysfunction (adjusted risk ratio 1.3, 95% CI 0.6– 2.4). Delirium was associated with early postoperative cognitive dysfunction, but the relationship of delirium to long-term postoperative cognitive dysfunction remains unclear.

Delirium has long been held to be a transient syndrome with complete resolution of symptoms following treatment of the underlying disorder [1]. The high incidence of postoperative delirium after elective, non-cardiac surgery (4–54%) [2], provides a useful clinical venue to study its relationship to postoperative cognitive and functional impairments [3–5]. Patients with delirium are at increased risk of long-term cognitive and functional decline [3,6,7].

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Delirium is defined as an acute change in cognition and attention. The study of delirium and its complications has been facilitated by the validation of reliable and accurate standardized instruments [8–10] (for example Confusion Assessment Method, Memorial Delirium Assessment Scale, Delirium Rating Scale, etc) derived from the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) [1,8–10]. The DSM identifies inattention as the key cognitive deficit in delirium [8] and we have recently demonstrated that pre-operative impairment in executive function and attention may predispose patients to delirium [11].

Postoperative Cognitive Dysfunction (POCD) has been best described after coronary artery bypass graft surgery and has been reported to occur in 53% of patients at discharge, 36% at 6 weeks, and 24% at 6 months [12]. The International Study of Postoperative Cognitive Dysfunction (ISPOCD) examined older, elective, non-cardiac surgery patients and found the incidence POCD to be 26% at 7 days and 10% at 3 months [13]. The definition of POCD remains controversial, and many different definitions have been used in the non-cardiac and cardiac surgical literature [14,15]. To assess POCD, patients are administered a battery of neuropsychological tests prior to and after surgery. The postoperative tests selected are variable and once testing is completed, the definitions of POCD attempt to reduce multiple neuropsychological test scores to a single dichotomous variable [15].

The relationship between postoperative delirium and POCD has not been previously examined with an extensive neuropsychological battery. The purpose of this study, therefore, was to determine if delirium and POCD are related events on a continuum of postoperative cognitive dysfunction, by performing a secondary analysis of the ISPOCD study data. Specifically, we hypothesised that patients with postoperative delirium are more likely to meet criteria for diagnosis of POCD and that subjects with long lasting delirium (≥3 days) are more likely to have early and long-term POCD.

Methods

Between November 1st 1994 and May 31st 1996 the International Study of Post Operative Cognitive Dysfunction (ISPOCD) recruited 1218 patients aged ≥60 who were undergoing non-cardiac surgery. The ISPOCD study recruited in eight countries (Denmark, France, Germany, Great Britain, Greece, Netherlands, Spain, United States) [13]. Patients were excluded if they had: a score of ≤23 on the Mini Mental State Examination (MMSE) [16], central nervous system disease including dementia or Parkinson's disease, previous neuropsychological testing, illiteracy, inability to understand the language of the test administration (English, Danish, Dutch, French, German, Greek, and Spanish), administration of tranquilizers or antidepressants prior to admission, cardiac or neurosurgery, severe hearing or vision disorders, life expectancy less than three months, or refusal to comply with the protocol. The protocol was approved by the Institutional Review Boards at all centers and all subjects provided written informed consent. The primary outcome of the ISPOCD study, POCD, has been previously described [13] and this secondary analysis examines the relationship of delirium and POCD.

Beginning on the operative day, a trained interviewer administered the orientation questions of the MMSE daily until postoperative day 3 and this was supplemented by scrutinizing the medical record and nurse chart to identify symptoms of delirium. From day 4 until discharge, the evaluation was based on the medical record and nurse chart. The interviewer recorded the presence or absence of delirium according to the criteria established in the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition (DSM-III) [17], including disturbance of attention developing over a short time with fluctuation over time, disorganized thinking, and other associated symptoms. The interviewers from all sites were trained in administration of the delirium and neuropsychological testing at a training meeting in Manchester, UK.

Whenever possible, the initial interviewer who performed the cognitive testing examined the patient after surgery. Adherence to the study protocol was monitored by regular visits from the steering committee. The duration of delirium was calculated by counting the days from which a subject developed delirium to the last day delirium was recorded. Those with delirium of three or more days were compared with those with delirium <3 days, based on a priori consensus of experts.

A battery of neuropsychological tests was completed upon entry into the study, postoperatively on the earlier of 7 days or hospital discharge, and at 3 months. The 45 min battery, administration protocol, and primary outcome (POCD) has been described in detail previously [13]. The battery was derived from standard, widely-administered neuropsychological tests that were translated into the native languages of the participating country and validated in the native language in a separate population [13]. In accordance with the ISPOCD study, we selected seven variables from four neuropsychological tests that had high correlation with age and IQ in a control population [13]. The Visual Verbal Learning Test, based on Rey's auditory recall of words [18], consists of 15 words presented at a fixed rate on a computer screen. At the end of the three learning trials and a 15–25 min delay, subjects were asked to recall as many words as possible. Variables selected for analysis were the number of words recalled over the three learning trials and the number of words recalled after a delay. The Concept Shifting Test, derived from the Trail-making Test [19], and the Stroop Color-Word interference test [20] are timed measures that consist of two priming trials followed by an interference trial. The time to complete and errors of the interference trials were selected for analysis. The Letter-Digit Substitution was based on the symbol-digit substitution task from the Wechsler Adult Intelligence Scale [21], from which the number of correct answers was recorded. Whenever possible, the initial interviewer also administered the follow-up battery. The ISPOCD study identified patients with POCD using a definition based on change from baseline which consisted of either a composite Z-score of >2 across tests or two or more tests with Z-scores >2 [13,14].

Prior to surgery, the age of the subjects and the years of education were collected from subjects. In previous analyses, age and education were associated with neurocognitive performance in control populations [13]. The duration of surgery was collected from the medical record.

Our bivariable analysis compared the risk of POCD at 7 days and 3 months when delirium was present with the risk of POCD when delirium was absent using a Chi square test. Crude relative risk (RR) estimates are presented with 95% confidence intervals (CI). Adjusted analyses used logistic regression to adjust for age, education, and duration of surgery. From the logistic regression, we used the adjusted odds ratio and 95% CI for delirium to calculate the adjusted relative risk using the method of Zhang and Yu [22]. All statistical analyses were performed using SPSS version 11.5.0 (SPSS, Inc, Chicago, USA). We used the Chi square test to calculate the risk for POCD in those with ≥3 days of delirium and those with <3 days of delirium. In the multivariable analysis, we used logistic regression to adjust for age, education, and duration of surgery and calculated an adjusted relative risk for POCD. For both timepoints, we calculated risk using only the subjects who completed the follow-up assessments.

Those subjects missing follow-up at either the 7 day or 3 month assessment were excluded from the analyses of POCD risk. This poses some challenges to our ability to draw conclusions. To analyze the effect of the missing data on our outcomes, we utilized the response probability ratio methodology described by Magder to examine bias in the missing data [23]. In addition, with the sample completing the 7 day and 3 month assessments, we calculated the power of our analyses to disprove the null hypothesis (that is, delirium is not associated with POCD)

Results

Figure 1 describes the follow-up testing of the 1218 subjects enrolled. Fifty-seven subjects (5%) did not have postoperative delirium assessments and neuropsychological follow-up was incomplete in 143 (16%) subjects at 7 days and in 215 (22%) at 3 months due to death, complications, refusal, and loss to follow-up [14]. Overall, the sample had a mean (SD) age of 68.7 (5.9) yr and had 10.1 (3.8) yr of education. There were slightly more males (53%) than females. Subjects underwent surgery for a mean duration of 149 (85) min. The mean preoperative MMSE score was 27.8 (1.6). Of the 99 patients with postoperative delirium (sample size = 1161), seventy-five (75%) completed 7 day cognitive testing (sample size = 1018), and sixty-one (62%) completed 3 month cognitive testing (see Table 1). Subjects who did not complete follow-up at 7 days and 3-months were significantly older, worse baseline cognitive performance and underwent surgery for a longer duration ($p<0.05$).

Table 2 describes the risk of POCD at 7 days and 3 months in those with and without delirium at any time within the postoperative period. In the 7 day analysis, after adjustment for age, education, and duration of surgery, the adjusted RR of POCD was 1.6 (95%CI 1.1–2.1). Twelve patients had delirium on postoperative day 7 and eight completed cognitive testing; seven of the eight had short-term POCD. At 3 months postoperatively, the adjusted RR of POCD was 1.3 (95%CI 0.6–2.4). Delirium was not systematically reassessed at 3 months.

Subjects with delirium were more than twice as likely to not complete postoperative cognitive testing at 7 days (RR 2.4, $p<0.01$) compared with those without delirium. At the 7 day assessment, the response probability ratio suggested that the missing at random assumption for those missing the 7 day assessment was acceptable. The power of the analyses at the 7-day POCD assessment was 0.92 (Type II error $(1-\beta) = 0.92$). These results suggest that missing data did not substantially impact our ability to draw conclusions about delirium and POCD at the 7-day assessment. The 3-month missing data describe a much different picture. Subjects with delirium were again more than twice as likely to not complete the testing at 3 months (RR 2.3, $p<0.01$). However, the response probability ratio suggested that the data was not missing at random and the power of the 3-month POCD assessment was 0.09. Thus, our ability to draw conclusions about the relationship of delirium to POCD at the 3-month assessment is severely limited.

Using the ISPOCD definition of POCD, we compared the increased incidence of POCD in those with delirium of ≥3 days and those with <3 days of delirium (Table 3). After adjustment for age, education, and duration of surgery, the risk of early POCD at 7 days in subjects with delirium ≥3 days duration was increased (adj. RR 2.2, 95%CI 1.2–3.1). Longer duration of delirium was not associated with long-term POCD at 3 months (adj. RR 1.6, 95%CI 0.4–4.8), though as shown above, power was severely limited for these analyses.

Discussion

This analysis investigated the relationship between postoperative delirium and POCD using neuropsychological testing in older patients undergoing non-cardiac surgery which was collected as part of ISPOCD. Our results indicate that patients with postoperative delirium have a higher incidence of early POCD, but we cannot draw any definitive conclusions about long-term POCD because of limited power and missing data. Consistent with our hypothesis, early POCD appears to be more common in subjects who develop long-duration (≥3 days) delirium.

Our results shed an interesting light on the relationship of delirium and POCD, but do not fully describe that relationship. The diagnosis of delirium is derived from criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders, and for the past 15 years, most studies on delirium have used these criteria. POCD, in contrast, lacks a uniform and widely accepted

set of criteria. POCD is assessed by performance on a complex battery of neuropsychological tests that evaluate numerous cognitive domains including attention, memory, executive function, visuospatial, psychomotor, and language function [24–26]. Efforts to standardize the definition of POCD are needed [15].

Within the DSM criteria, inattention is identified as the cornerstone cognitive impairment of delirium. While the DSM criteria also examine other aspects of consciousness and thought, the focus on inattention allows targeted assessment which is available at the bedside. Because attention is important for optimal performance on all neuropsychological tests [27], delirium and POCD are not necessarily independent conditions. In some cases, delirium may be an important cause of POCD or the conditions may coexist in others.

Our finding of the significant association between delirium and short-term POCD, particularly in those subjects with delirium for more than three days, suggest that attention deficits may place delirium and POCD on a continuum of the postoperatively disordered brain. Failure to recover from delirium quickly may be indicative of a brain that is vulnerable to the cognitive effects of surgery. However, there may be other factors involved, because not all subjects who developed delirium went on have short-term POCD. Finally, the causal link between delirium and short term POCD remains to be established.

In this study, subjects with delirium were at twice the risk of not completing the 7-day and 3-month assessments. We demonstrated that the 3-month data were not missing at random and thus a systematic bias may exist causing patients with delirium (or the complications thereof) not to return for follow-up. As postoperative delirium has been associated with increased morbidity, mortality, costs, and functional deficits [3,4,28,29], this is not unexpected. Such a bias would skew our results toward the null (no association with delirium and POCD) as was demonstrated in the non-significant association of delirium and long-term POCD. While postoperative delirium may be associated with long-term cognitive deficits, our ability to draw conclusions about the relationship of delirium and long-term POCD is limited in the present study.

The strengths of this study include the detailed and complete nature of the neuropsychological testing. The prospective study performed neuropsychological assessment on most subjects at baseline (98%), 7 days after surgery (84%) and 3 months after surgery (78%). The delirium assessments were completed on 96% of subjects. Subjects with dementia and cognitive impairment at baseline (MMSE <24) were excluded, which minimized, but not eliminated the ‘floor effects’ of patients with poor cognitive function.

A major limitation of this study is the assessment for delirium. Firstly, there was no systematic pre-operative delirium assessment. However, patients with baseline cognitive impairment (MMSE<24) were excluded and all subjects were able to complete a neuropsychological battery which requires intact attention. Thus, we believe that the probability of delirium at baseline is exceedingly low. Next, the methods to assess delirium are suboptimal when compared with current standards. The diagnostic criteria of delirium have increased sensitivity and specificity when completed following a formal mental status interview with assessment of attention and completion of a standardized delirium instrument [30]. The ISPOCD assessment used the orientation items of the MMSE but did not use a specific delirium instrument or include an assessment of attention. As a result, we believe that the delirium is under-recognized in this study. This under-recognition would result in mis-classification of some delirium cases as non-delirium which would tend to bias our results against seeing a significant association. Thus, the finding of a positive association of delirium with short-term POCD is likely to be robust. Additionally, this study would have benefited from assessment of inter-rater reliability to ensure good agreement between interviewers and test-retest

reliability for practice effects with the delirium assessment. In previous work, the MMSE has been shown to have limited practice effects [31]. Delirium was not the primary outcome measure of the ISPOCD study. However, the standardised method of assessment provides a consistent estimate of the relationship of delirium and POCD.

There are other limitations of this study that require comment. Because subjects with delirium were more likely to miss postoperative neuropsychological testing, the association of delirium and POCD may be underestimated. Additionally, the study began enrolling subjects over 10 yr ago and improvements in peri-operative care may have reduced the incidence of delirium and POCD. While patients with use of major tranquilizers or antidepressants, alcohol abuse, or substance abuse were excluded from the study, we are unable to fully adjust for all preoperative and intra-operative factors which may predispose or precipitate delirium. However, given that this study is primarily focused on the outcomes of delirium, controlling for antecedent factors is not as critical for this analysis, and this limitation does not threaten the internal validity of our findings. This study did not address the temporal relationship of delirium onset to POCD. The overlap between delirium on postoperative day 7 and short-term POCD limits our ability to fully separate these conditions. However, this does support the hypothesis that delirium and short-term POCD are on a continuum of the postoperative disorganized brain. Finally, whereas peri-operative delirium has clear clinical and economic relevance [3,4,28], the clinical and functional impact of early and long-term POCD remains uncertain.

In the largest study of the relationship of delirium and POCD, we determined that delirium is associated with POCD 7 days after surgery, especially in those with delirium for ≥3 days. Subjects with delirium were significantly less likely to complete follow-up at the 3 months assessment, limiting our ability to draw conclusions about the associations of delirium with long-term POCD. Further studies investigating the relationship between delirium and POCD are necessary to enable design of effective interventions to reduce the long-term adverse cognitive and functional sequelae of surgery among vulnerable elders.

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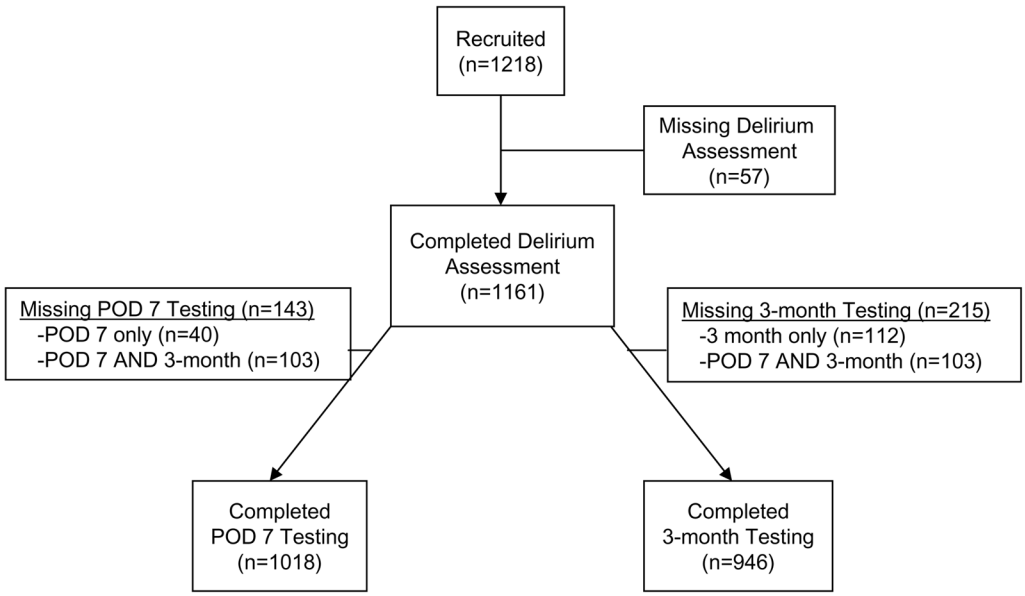

Figure 1.

Table 1

Population comparison of those with completed testing at each stage. Values are mean (SD)

Characteristic	Completed postoperative delirium assessment		Completed postoperative day 7 cognitive assessment		Completed 3-month cognitive assessment	
	yes n = 1161	no n = 57	yes n = 1018	no n = 143	yes n = 946	no n = 215
Age (yr)	68.9 (5.9)	69.6 (6.7)	68.7 (5.9)	70.1 (5.9)*	68.6 (5.9)	70.2 (6.1)*
Male	618 (53%)	31 (54%)	535 (53%)	83 (58%)	483 (51%)	135 (63%)*
Education (yr)	10.0 (3.8)	10.1 (4.3)	10.1 (3.8)	9.4 (3.6)*	10.1 (3.8)	9.4 (3.8)*
Surgery duration (min)	151 (86)	186 (127)*	149 (85)	169 (90.4)*	148 (84)	163 (94)*
MMSE†	27.8 (1.6)	28.2 (1.4)*	27.8 (1.6)	27.5 (1.7)*	27.9 (1.6)	27.5 (1.7)*
Developed postoperative delirium (%)	99 (8%)	n/a	75 (7%)	24 (17%)*	61 (6%)	38 (18%)*

* p <0.05 when compared to those who completed testing

† MMSE, Mini-Mental State Examination

Table 2

The association of delirium and postoperative cognitive dysfunction. The relative risks (RR) presented compare the risk of POCD in those with and without delirium at any time within the postoperative period. Values are number (%), or RR (95% CI)

7-days after surgery (n = 1018)				3-months after surgery (n = 946)			
POCD when:		Crude RR	Adjusted RR †	POCD when:		Crude RR	Adjusted RR †
Delirium present (n = 75)	Delirium absent (n = 943)			Delirium present (n = 61)	Delirium absent (n = 883)		
33 (44%)	232 (25%)	1.8 (1.4–2.4)*	1.6 (1.1–2.1)*	9 (15%)	85 (10%)	1.5 (0.8–2.9)	1.3 (0.6–2.4)

* p <0.05

† Relative risk adjusted for age, education, and duration of surgery with logistic regression using the method of Zhang and Yu [22].

Table 3

Association between the risk for postoperative cognitive dysfunction and the duration of delirium. Values are numbers, or relative risk (95% CI)

		Risk of postoperative cognitive dysfunction				
		7-day postoperative assessment			3-month postoperative assessment	
Duration of delirium	**n**	**Crude RR**	**Adjusted RR †**	**n**	**Crude RR**	**Adjusted RR †**
≥3 days	18	2.5 (1.7–3.6)*	2.2 (1.2–3.1)*	12	1.7 (0.5–6.3)	1.6 (0.4–4.8)
<3 days	57	1.6 (1.1–2.2)*	1.4 (0.9–2.0)	49	1.5 (0.7–3.0)	1.2 (0.6–2.5)

* $p < 0.05$

† Adjusted for age, education, and duration of surgery with logistic regression using the method of Zhang and Yu [22]